Remarks

Upon entry of this amendment claims 15, 62, 65 and 66 are pending in the instant application. Support for the amendment to claim 15 can be found in the specification as originally filed at page 1, line 32 to page 2, line 2 and paragraphs 17 and 19 of the published application. Support for amendment to claim 65 is found in the in the specification as originally files, for example at paragraph [0026] to [0030] (Example 5) of the published application, wherein Applicants assay the growth of NIH3T3 cells with transfected sense ZNFNA31, antisense ZNFNA31, and mock vectors.

1. Priority

Applicants do not wish to challenge the Examiner's assertion that the first disclosure of the use of siRNA as claimed occurs in 60/450,644 filed February 28, 2003. However, Applicants disagree with the Examiners assertion that the prior disclosures fail to provide adequate support or enablement for the methods steps wherein "control cells that do not express the protein comprising SEQ ID NO: 2" are cultured in the presence of test compounds and then detected for proliferation (i.e., the use of negative controls). As noted below, Applicants respectfully submit with the use of "negative controls" not only finds support in the instant application (filed 02/27/04) but further supported by Provisional Application 60/450,644 filed February 28, 2003. Accordingly, Applicants submit that the instantly claimed invention should be afforded a priority date of February 28, 2003.

2. Claim Rejections- 35 U.S.C 112, first paragraph

Written Description/New Matter:

Claims 15, 62, 65 and 66 have been rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. According to the Examiner, the specification fails to provide written description for the limitation "control cells that do not express the protein comprising SEQ ID NO:2. Applicants disagree.

Applicants submit that these grounds of rejection are improper under the standard set forth by the Court of Customs and Patent Appeals in *Wertheim.* The Court in *Wertheim* unambiguously held that literal "*haec verba*" or "*ipsis verbis*" support required or compliance

with the written description requirement of Section 112. *In re Wertheim*, 541 F.2d at 265 (citing *In re Lukach* 442 F.2d 967, 969 (C.C.P.A. 1971)). See also M.P.E.P. §2163.02, which clearly states that the "subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement."

Instead, the inquiry is whether one following Applicant's specification would necessarily select the later claimed subject matter. See *Staehelin v. Secher*, 24 U.S.P.Q.2d 1513, (Bd. Pat. App. & Int. 1992) and *Freerksen v. Gass*, 21 U.S.P.Q.2d 2007 (B.P.A.I. 1990). The question, therefore, is whether the originally filed application would have conveyed to a person of ordinary skill in the art that Applicants invented the subject matter later claimed by them including the limitations in question. *In re Smythe*, 480 F.2d 1376, 178 U.S.P.Q. 279 (C.C.P.A. 1973).

In this case, the question is whether the originally filed specification implicitly or impliedly conveys to the skilled artisan the use of a particularly designed control (i.e., a control cell that does not express a protein comprising the amino acid sequence of SEQ ID NO: 2) in the context of the method of the present claims in order to determine if a particular test compound is a specific inhibitor of ZNFN3A1 (SEQ ID NO: 2) (as opposed to a general proliferation inhibitor). The findings of the present invention indicate that ZNFN3A1 (SEQ ID NO: 2) confers oncogenic activity to cancer cells through the transcriptional activation of downstream target genes and that inhibition of this activity presents a promising strategy for the treatment of cancer, particularly HCC.

It is a goal of the present invention to identify specific inhibitors of ZNFN3A1, more particularly those that inhibit its proliferative potential. Though the instant specification does not explicitly describe a control as claimed in the context of the enumerated experimental examples, such scientific controls are a recognized in the art as a vital part of the scientific method and necessary to eliminate alternate explanations of experimental results.

Accordingly, Applicants submit that disclosures of the instant specification, particularly the disclosures of Example 5 (which compares the growth potential of sense ZNFN3A1-transfected NIH3T3 cells with NIH3T3 control cells transfected with antisense-ZNFN3A1 and mock vectors), and Example 6 (which compares the growth potential of various HCC that endogenously express ZNFN3A1 transfected with various antisense inhibitors (e.g., test compounds comprising RNAi) to those transfected with control "mock" vector), coupled with

conventional knowledge in the art regarding the necessity of proper experimental controls, provide inherent support for the previously presented limitations to claims 15 and 65.

Furthermore Applicants submit that in the context of assaying for specific inhibitors, one skilled in the art would have understood, at the time the patent application was filed, the control cells as presently claimed to be optionally present. Accordingly, the inclusion of "control cells that do not express the protein comprising the amino acid sequence of SEQ ID NO: 2" in the method of the present claims does not constitute new matter. Applicants request that this rejection be withdrawn.

Enablement:

Claims 15, 63, and 65 have been rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement. According to the Examiner, although the specification enables methods of screening RNAi that inhibit the activity/expression of the ZNFN3A1 protein of SEQ ID NO: 2 in congenic mammalian cells, it does not reasonably enable methods of screening for any other test compound "which binds to the protein or inhibits expression of the protein". Accordingly, the Examiner concludes that the specification does not enable a person skilled in the relevant art to make or use the invention commensurate in scope with the pending claims. Applicants disagree.

We wish to direct the Examiner's attention to Example 17 of the Revised Written Description Training Materials. While the requirement for an adequate written description and an enabling disclosure are two separate requirements, there is nevertheless often significant overlap between the two requirements. Accordingly, while Example 17 of the Revised Written Description Training Materials addresses a written description rejection, the conclusions asserted in the context of this example are also relevant to an enablement analysis. For example, like Applicants' claims 15 and 65, claim 2 of Example 17 (set forth below) is directed to a method of identifying a particular compound (i.e., a "test compound") as an inhibitor of a particular activity (i.e., inhibiting POPKIN-2 activity vs. inhibiting cell proliferation promoting activity) of a particular reference protein (i.e., POPKIN-2 vs. ZNFN3A1) by (a) contacting (culturing) test cells that express the referenced protein and control cells with the particular test compound and (b) comparing the respective activities measured.

Claim 2: A method for identifying a compound that selectively inhibits POPKIN-2 activity comprising

(a) contacting a test compound with a cell expressing POPKIN-2 but not POPKIN-1 and measuring POPKIN-2 activity,

(b) comparing the measured activity from step a to the activity of POPKIN-2 in a non-contacted control cell,

and if the measured activity of step a is less than the measured activity of POPKIN-2 in the control cell then,

(c) contacting the compound with a cell expressing POPKIN-1, but not POPKIN-2 and measuring POPKIN-1 activity, and

(d) comparing the measured POPKIN-1 activity from step c to the activity of POPKIN-1 in a non-contacted control cell,

wherein, if the measured POPKIN-1 activity of contacted and control cells is the same, a compound that selectively inhibits POPKIN-2 is identified.

In determining whether above claim 2 met the written description requirement, the USPTO concluded that although "the specification does not describe the complete structure, partial structures, physical properties or chemical properties of a compound that selectively inhibits POPKIN-2 activity, nor does the specification describe any correlation between the sequences of POPKIN-1 and POPKIN-2 and the structure of any compounds that would selectively inhibit POPKIN-2 activity", it "does describe the claimed method of screening compounds for selective inhibition of POPKIN-2 activity, reciting the instant steps for identifying a compound with the desired activity".

Notwithstanding the noted deficiencies, the USPTO asserts that the level of skill and knowledge in the art as such that "one would be able to follow the detailed steps of the claimed method", noting that the "practice of the method require no knowledge of structures and properties of a compound that would predictably result in the desired activity" and that the invention is directed to a "screening process" and "not the compounds screened or the compounds identified via the claimed process". The USPTO thus concludes that one of ordinary skill in the art find applicant to have been in possession of the claimed method.

From the findings of Example 17, one must conclude that it is not necessary to describe the structure or properties of ANY compound that selectively inhibits a reference activity, nor is it necessary to describe ANY correlation between the sequences of the reference proteins and the

structure of any compounds that would selectively inhibit the activity thereof in order to adequately describe such a screening assay.

In addition, assuming we afford a consistent characterization the level of skill and knowledge in the art as being such that the practice of screening assays such as set forth in Example claim 2 (or Applicants' claim 15) "require no advance knowledge of structures and properties" of compounds to being assayed and subsequently identified, Applicants submit that in addition to finding an applicant to be in possession of such a method, one of ordinary skill in the art must likewise be found to be able to practice the invention in accordance with the full breadth of its claims, without undue experimentation.

Thus, the requirement that the Applicants' to describe a plurality of divergent working examples of ZNFN3A1 inhibitors, in addition to the numerous antisense and interference RNA examples already provided, in order to enable the invention of the pending claims is inconsistent with the findings of Example 17.

With respect to the Examiner's ongoing challenge to enablement on the grounds that the invention of the pending claims may give rise to false positive designations, Applicants note that the Examiner initially rejected the claimed methods for failing to provide a nexus or link between any observed differences in proliferation due to the compound and ZNFN3A1, noting that broad spectrum anti-proliferative compounds like doxorubicin and anthracycline could be incorrectly labeled as inhibitors of ZNFN3A1. To address the Examiner's concern, Applicants amended the claims to compare the proliferation of test cells that express ZNFN3A1 with control cells that did not express ZNFN3A1. Thus, the potential for false positive, with the exception of reasonable experimental error, is eliminated. However, the Examiner continues to allege a potential for false designation of a compound as a ZNFN3A1 inhibitor when "other, more plausible, explanations exist for the differences found in proliferation".

Not only do Applicants disagree with the Examiner's suggestion but Applicants further wish to remind the Examiner that the fact that a generic claim *might* encompass some possibly inoperative embodiments is not enough in itself to render the claim unpatentable. *Atlas Powder v. E.I. Dupont de Nemours*, 750 F.2d 1569, 1576 (Fed. Cir. 1984).

Furthermore, Applicants respectfully submit that the Examiner's suggestion that the pending claims permit the use of "any" test cell and "any" control cell is in error. As amended

herewith, the claims require the use of either mammalian test and control cells, wherein the test cell expresses ZNFN3A1 while the control cell does not (i.e., claim 15), or the use of identical test and control cells differing only in that the test cell has been genetically engineered to express ZNFN3A1 (transfected with a vector comprising a nucleotide sequence that encodes the protein of SEQ ID NO: 2) (i.e., claim 65). Thus, Applicants submit that there is no possibility for the as-claimed screening methods to give rise to false positive results; a differential reduction in proliferation cannot arise through inhibition a general pathway but instead must result from the specific inhibition of the ZNFN3A1 pathway.

The Examiner has further rejected the claimed subject matter for failing to disclose in the specification an assay for assessing the proliferation activity of ZNFN3A1 or the inhibition thereof. Applicants wish to direct the Examiner's attention to paragraph [0045] of the published application wherein the expression of ZNFN3A1 is directly linked to an increase in cell growth and its corresponding suppression of its expression is directly linked to significant growth-inhibition of hepatoma cells. Therein, the proliferation activity of ZNFN3A1 is characterized as resulting from the "transcriptional activation of target genes including EGFR through a complex with RNA helicase and RNA polymerase II". Accordingly, Applicants respectfully submit that one can readily measure the proliferation activity of ZNFN3A1 (and the inhibition thereof) by assaying for the presence, absence or inhibition of complex formation as described in the as-file specification.

In conclusion, Applicants have provided ample and adequate working examples, substantially eliminated the potential for false positive results, and provided a measurable criteria for determining the inhibition of the proliferation activity of ZNFN3A1, that one reasonably skilled in the art could practice the claimed invention from the disclosures in the specification, coupled with information known in the art, without undue experimentation. Accordingly, Applicants request reconsideration and withdrawal of the enablement rejections in view of the amendments and remarks presented herein.

3. Claim Rejections - 35 U.S.C. §112, second paragraph

Claims 63-66 stand f rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. According to the Examiner, the recitation of "the test compound which binds to the protein, or inhibits the expression of the protein" lacks antecedent basis. Claims 63 and 64 have been canceled. Thus rejection is moot with respect to those claims. Claims 65 and 66 have

been amended to recite "a test compound which binds to the protein, or inhibits the expression of the protein" Applicants submit that claims 64 and 65 as amended are definite. This rejection should be withdrawn.

CONCLUSION

Applicant respectfully submits that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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